

# 107217

## SEARCH REQUEST FORM

Access DB#

RECEIVED

Scientific and Technical Information Center

OCT 31 2003

Requester's Full Name: MOLLY CEPERLEY Examiner #: 59257 Date: 10/31/03  
 Art Unit: 1641 Phone Number 30 8-4239 Serial Number: 10/025 378  
 Mail Box and Bldg/Room Location: 8D15 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*  
 Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Tertiary Amine Compounds for use in Immunoassays

Inventors (please provide full names): Christopher C. Lawrence, Armen B. Shanafelt

Earliest Priority Filing Date: 12/18/01

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search for particle agglutination assays which use a tertiary amine (formula (I) of claim 1) to avoid non-specific binding.

Prefer latex particles which have been activated by a carbodiimide (CDI).

Please also search the use of the tertiary amines listed in Table A of pages 18+19. (These may not fit the definitions of the tertiary amines in claim 1.).

Terms: latex agglutination, particle agglutination, ~~carbodiimide~~ carbodiimide activation, immunoassay, antibody, interference reduction, non-specific binding, unspecific binding.

Particle types: polystyrene, poly(methylmethacrylate) (PMMA), gold (nanoparticles and colloids), silica, glass, ceramics, alumina

### STAFF USE ONLY

|  | Type of Search         | Vendors and cost where applicable |
|--|------------------------|-----------------------------------|
| Searcher: _____                        | NA Sequence (#) _____  | STN <u>711.99</u>                 |
| Searcher Phone #: _____                | AA Sequence (#) _____  | Dialog _____                      |
| Searcher Location: _____               | Structure (#) <u>1</u> | Questel/Orbit _____               |
| Date Searcher Picked Up: <u>11/10</u>  | Bibliographic _____    | Dr. Link _____                    |
| Date Completed: <u>11/10</u>           | Litigation _____       | Lexis/Nexis _____                 |
| Searcher Prep & Review Time: <u>30</u> | Fulltext _____         | Sequence Systems _____            |
| Clerical Prep Time: _____              | Patent Family _____    | WWW/Internet _____                |
| Online Time: <u>47</u>                 | Other _____            | Other (specify) _____             |



# STIC SEARCH RESULTS FEEDBACK FORM

## Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact*:

Mary Hale, Information Branch Supervisor  
308-4258, CM1-1E01

## Voluntary Results Feedback Form

➤ I am an examiner in Workgroup:  Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature  
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library CM1 – Circ. Desk



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L4

STR

4  
G1  
}  
G1~N~G1  
1 2 3

Ak~G2  
@5 6

Ak~O~Ak~G2  
@7 8 9 10

O~Ak  
@11 12

S~Ak  
@13 14

O~C~O  
15 @16 17

O~C~O~Ak  
18 @19 20 21

O~C~N~Ak  
22 @23 24 25

VAR G1=5/7

VAR G2=OH/11/13/16/19/23

NODE ATTRIBUTES:

CONNECT IS E3 RC AT 2  
CONNECT IS E2 RC AT 5  
CONNECT IS E2 RC AT 7  
CONNECT IS E2 RC AT 9  
CONNECT IS E1 RC AT 12  
CONNECT IS E2 RC AT 13  
CONNECT IS E1 RC AT 14  
CONNECT IS E1 RC AT 17  
CONNECT IS E1 RC AT 21  
CONNECT IS E2 RC AT 24  
CONNECT IS E1 RC AT 25

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L6 405652 SEA FILE=REGISTRY ABB=ON PLU=ON (((N AND C AND O AND H)/ELS  
AND 4/ELC.SUB) OR ((N AND C AND S AND H)/ELS AND 4/ELC.SUB) OR  
((N AND C AND O AND S AND H)/ELS AND 5/ELC.SUB)) AND NC=1 NOT  
RSD/FA

L11 651 SEA FILE=REGISTRY SUB=L6 SSS FUL L4

L14 1 SEA FILE=HCAPLUS ABB=ON PLU=ON 2003:488678/AN

L15 23324 SEA FILE=HCAPLUS ABB=ON PLU=ON L11

L16 23324 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 OR L15

L17 47217 SEA FILE=HCAPLUS ABB=ON PLU=ON IMMUNOASSAY+OLD,NT/CT

L18 55 SEA FILE=HCAPLUS ABB=ON PLU=ON L16 AND L17

L19 707 SEA FILE=HCAPLUS ABB=ON PLU=ON CARBODIIMIDE/CT

L20 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L18 AND (L19 OR CARBODIIMID?  
OR CDI)

L21 6651 SEA FILE=HCAPLUS ABB=ON PLU=ON "AMINES (L) TERTIARY"/CT

L25 1317 SEA FILE=HCAPLUS ABB=ON PLU=ON "IMMUNOASSAY (L) AGGLUTINATION  
TEST"+OLD/CT

L26 5 SEA FILE=HCAPLUS ABB=ON PLU=ON (L16 OR L21) AND L25

L27 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L20 OR L26

L28 11 SEA FILE=HCAPLUS ABB=ON PLU=ON (L16 OR L21) AND (LATEX OR  
PARTICL?) (3A)AGGLUT?

L29 12 SEA FILE=HCAPLUS ABB=ON PLU=ON L27 OR L28

*all considered  
03/02/04  
MEC*

=&gt; d 129 ibib abs hitind hitstr 1-12

L29 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:488678 HCAPLUS

DOCUMENT NUMBER: 139:49497

TITLE: Tertiary amine compounds for use in immunoassays

INVENTOR(S): Lawrence, Christopher C.; Shanafelt, Armen B.

PATENT ASSIGNEE(S): Roche Diagnostics GmbH, Germany; F. Hoffmann-La Roche AG

SOURCE: Eur. Pat. Appl., 13 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.  | KIND | DATE             | APPLICATION NO. | DATE       |
|---|------|------------------|-----------------|------------|
| EP 1321770  | A2   | 20030625         | EP 2002-27992   | 20021214   |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK |      |                  |                 |            |
| US 2003138974   | A1   | 20030724         | US 2001-25378   | 20011218   |
| JP 2003207512   | A2   | 20030725         | JP 2002-363686  | 20021216   |
| PRIORITY APPLN. INFO.:  |      |                  | US 2001-25378   | A 20011218 |
| OTHER SOURCE(S):  |      | MARPAT 139:49497 |                 |            |

AB A reagent for use in immunoassays reduces interference in **particle agglutination** assays. The reagent contains particles having covalently bound antibodies and a tertiary amine compd. of formula (I): N(R1-X)(R2-Y)(R3-Z). The moieties R1, R2, and R3 are independently alkyl or alkyl ether. The moieties X, Y, and Z are independently -OH, -O-R4, -S-R4, -C(=O)-OH, -C(=O)-OR4, or -C(=O)-NHR4 and R4 is alkyl. Triethanolamine gave improved performance in **latex agglutination** immunoassays.

IC ICM G01N033-53

ICS G01N033-543

CC 9-10 (Biochemical Methods)

ST tertiary amine reducing interference **particle agglutination** immunoassay; **latex agglutination** immunoassay triethanolamine reducing nonspecific binding

IT **Immunoassay**  
(**agglutination test**; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)

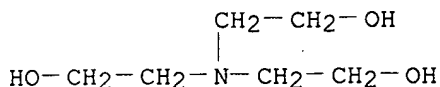
IT Antibodies  
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
(immobilized; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)

IT **Immunoassay**  
(**latex agglutination test**; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)

IT Antibodies  
RL: ARG (Analytical reagent use); RCT (Reactant); ANST (Analytical study); RACT (Reactant or reagent); USES (Uses)  
(monoclonal, latex particles sensitized with; tertiary amine compds.)

- for reducing interference in **particle agglutination** immunoassays)
- IT **Carbodiimides**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (particle surface activation with; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT Latex  
 (particles; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT **Amines, preparation**  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (reaction products, with succinimide esters, on particle surface; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT Blood analysis  
 Immobilization, molecular  
**Immunoassay**  
 Microparticles  
 Test kits  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT **Amines, analysis**  
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)  
 (tertiary; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT Particles  
 (with immobilized antibodies; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT 459-73-4DP, Glycine ethyl ester, reaction products with succinimide ester 929-06-6DP, reaction products with succinimide ester 929-59-9DP, 2,2'-(Ethylenedioxy)bisethylamine, reaction products with succinimide ester 4246-51-9DP, 4,7,10-Trioxa-1,13-tridecanediamine, reaction products with succinimide ester  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (on particle surface; tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT 1403-66-3, Gentamicin  
 RL: ANT (Analyte); ANST (Analytical study)  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT 102-71-6, Triethanolamine, analysis 104-78-9, 3-Diethylaminopropylamine 109-54-6, Dimethylaminopropylchloride 109-55-7, 3-Dimethylaminopropylamine 121-44-8, Triethylamine, analysis 32897-26-0, 1-Ethyl-3-(3-dimethylaminopropyl)urea  
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT 633-96-5 929-06-6 1892-57-5, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide 6066-82-6, N-Hydroxysuccinimide  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)
- IT 123-56-8DP, Succinimide, esters, reaction products with primary amine on particle surface

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)  
 IT 102-71-6, Triethanolamine; analysis  
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)  
 (tertiary amine compds. for reducing interference in **particle agglutination** immunoassays)  
 RN 102-71-6 HCAPLUS  
 CN Ethanol, 2,2',2''-nitrilotris- (9CI) (CA INDEX NAME)



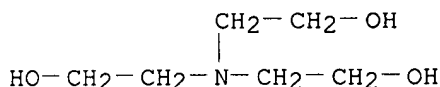
L29 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 2003:355758 HCAPLUS  
 DOCUMENT NUMBER: 138:350816  
 TITLE: Particles for immunoassays and methods for treating the same  
 INVENTOR(S): Lawrence, Christopher C.; Yuan, Wei; Shanafelt, Armen B.  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 53,058.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE        |
|---|------|----------|-----------------|-------------|
| US 2003087458   | A1   | 20030508 | US 2001-25196   | 20011218    |
| US 2003092201   | A1   | 20030515 | US 2001-53058   | 20011102    |
| EP 1319953  | A1   | 20030618 | EP 2002-24080   | 20021029    |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK |      |          |                 |             |
| JP 2003185667   | A2   | 20030703 | JP 2002-318893  | 20021031    |
| PRIORITY APPLN. INFO.:  |      |          | US 2001-53058   | A2 20011102 |
|   |      |          | US 2001-25196   | A 20011218  |

OTHER SOURCE(S): MARPAT 138:350816  
 AB A method of treating particles to be used in immunoassays reduces interference in **particle agglutination** assays. For particles having covalently bound antibodies and residual NHS-ester or sNHS-ester groups on the surface, the reactive esters are treated with an aq. mixt. contg. an amine compd. of formula (I): 2 The moiety -X is -NH<sub>2</sub>, -OH, or -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; and R is an alkyl group or an alkyl ether group. When -X is -NH<sub>2</sub> or -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, R contains from 1 to 20 carbon atoms; and when -X is -OH, R contains from 4 to 20 carbon atoms.  
 ICM G01N033-543  
 ICS G01N033-545; B05D003-00  
 NCL 436523000; 427002110  
 CC 9-10 (Biochemical Methods)  
 IT **Immunoassay**

**(agglutination test, Particle;****particles** for immunoassays and methods for treating the same)

- IT Adsorption  
 Alkyl groups  
 Amino group  
 Blood serum  
 Ceramics  
 Chemical formula  
 Coupling agents  
 Hydroxyl group  
**Immunoassay**  
 Interference  
 Latex  
 Mixtures  
 Particles  
 Surface  
 Test kits  
 pH  
 (particles for immunoassays and methods for treating the same)
- IT **Carbodiimides**  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (particles for immunoassays and methods for treating the same)
- IT 79-09-4D, Propanoic acid, amines contg. **102-71-6**,  
 Triethanolamine, reactions 123-56-8D, Succinimide, esters 459-73-4,  
 Glycine ethyl ester 929-06-6 929-59-9, 2,2'-  
 (Ethylenedioxy)bisethylamine 4246-51-9, 4,7,10-Trioxa-1,13-  
 tridecanediamine 6066-82-6, N-Hydroxysuccinimide 7440-44-0D, Carbon,  
 amines contg. 7782-44-7D, Oxygen, compd. contg. 82436-78-0,  
 N-Hydroxysulfosuccinimide  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (particles for immunoassays and methods for treating the same)
- IT **102-71-6**, Triethanolamine, reactions  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (particles for immunoassays and methods for treating the same)
- RN 102-71-6 HCAPLUS
- CN Ethanol, 2,2',2''-nitrilotris- (9CI) (CA INDEX NAME)



L29 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:31752 HCAPLUS

DOCUMENT NUMBER: 136:82290

TITLE: Insoluble carrier particle nephelometric immunoassay reagent

INVENTOR(S): Shigenobu, Kayoko; Oguri, Kazuhito

PATENT ASSIGNEE(S): Kyowa Medex Co., Ltd., Japan

SOURCE: PCT Int. Appl., 34 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

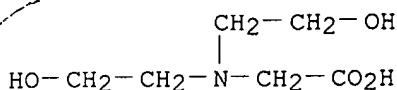
| PATENT NO.   | KIND   | DATE     | APPLICATION NO. | DATE       |
|--|--|----------|-----------------|------------|
| WO 2002003068  | A1   | 20020110 | WO 2001-JP5115  | 20010615   |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,<br>CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,<br>HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,<br>LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,<br>SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,<br>YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM<br>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,<br>DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,<br>BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG |  |          |                 |            |
| AU 2001064293  | A5   | 20020114 | AU 2001-64293   | 20010615   |
| EP 1298438   | A1   | 20030402 | EP 2001-938686  | 20010615   |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,<br>IE, SI, LT, LV, FI, RO, MK, CY, AL, TR   |  |          |                 |            |
| US 2003143758  | A1   | 20030731 | US 2002-312328  | 20021226   |
| PRIORITY APPLN. INFO.:   |  |          | JP 2000-198831  | A 20000630 |
|  |  |          | WO 2001-JP5115  | W 20010615 |
| OTHER SOURCE(S): MARPAT 136:82290  |  |          |                 |            |
| AB   | An insol. carrier particle nephelometric immunoassay reagent or kit is provided, which produces an accurate measurement results due to the stabilized absorbance of a reaction liq. caused by stabilizing an agglutination reaction of insol. carrier particles such as latex by suppressing the function of a blood plasma component which participates in the agglutination reaction, and thereby, affects on the measurement values. An insol. carrier particle nephelometric immunoassay method using this reagent or kit is also provided. In this method, an antigen or antibody in a sample is quantitated by the processes of (1) immobilizing the antigen or antibody on the insol. carrier particles <u>in the presence or absence of a buffer contg. a compd. possessing in the mol. the groups indicated in HOCH2CR2(R3)N(R1)CH2CO2H</u> (I, <u>R1</u> , <u>R2</u> and <u>R3</u> may be the same or different from one another, and independently represent a H, a <u>hydroxyalkyl group or the like</u> ; e.g., bicine, tricine); (2) performing an immuno-agglutination reaction by contacting a test sample with the antibody- or antigen-sensitized insol. carrier particle suspension in the presence of I; and (3) measuring the turbidity generated by the insol. carrier <b>particle agglutination</b> reaction. |          |                 |            |
| IC   | ICM G01N033-543<br>ICS G01N033-58; G01N033-53  |          |                 |            |
| CC   | 9-10 (Biochemical Methods)   |          |                 |            |
| IT   | <b>Agglutination</b><br>Blood plasma<br>Buffers<br>Carriers<br>Immobilization, molecular<br>Latex<br>Particles<br>Suspensions<br>Test kits<br>Turbidity<br>(insol. carrier <b>particle</b> nephelometric immunoassay reagent)  |          |                 |            |
| IT   | 150-25-4, Bicine 5704-04-1, Tricine<br>RL: ARU (Analytical role, unclassified); ANST (Analytical study)<br>(insol. carrier particle nephelometric immunoassay reagent)   |          |                 |            |
| IT   | 150-25-4, Bicine   |          |                 |            |



RL: ARU (Analytical role, unclassified); ANST (Analytical study)  
(insol. carrier particle nephelometric immunoassay reagent)

RN 150-25-4 HCAPLUS

CN Glycine, N,N-bis(2-hydroxyethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:42620 HCAPLUS

DOCUMENT NUMBER: 130:92468

TITLE: Methods for covalent immobilization of biomolecules to  
a carrier by means of a His-tag

INVENTOR(S): Bosman, Alfons; Van Wijnendaele, Frans; Van Den  
Broeck, Dirk; Van De Voorde, Andre

PATENT ASSIGNEE(S): Innogenetics N.V., Belg.

SOURCE: PCT Int. Appl., 34 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE   | APPLICATION NO. | DATE     |
|------------|------|--|-----------------|----------|
| WO 9900670 | A1   | 19990107   | WO 1998-EP3883  | 19980625 |
| W:         |      | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |                 |          |
| RW:        |      | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG   |                 |          |
| AU 9887290 | A1   | 19990119   | AU 1998-87290   | 19980625 |
| AU 746325  | B2   | 20020418   |                 |          |
| EP 991944  | A1   | 20000412   | EP 1998-938647  | 19980625 |
| R:         |      | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |                 |          |

PRIORITY APPLN. INFO.:

EP 1997-870095 A 19970625

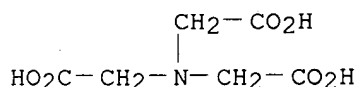
WO 1998-EP3883 W 19980625

AB The present invention relates to methods for covalent immobilization of biomols. to carriers and membranes, wherein the presence of a His-tag is exploited, and wherein the amino acid residues that comprise said His-tag are directly involved in the covalent bond. The present invention also provides several strategies that further augment the probability of covalent immobilization through said His-tags, such as improving the presentation of said His-tag, choosing the appropriate reaction conditions such as pH, temp., concn. of reagent and kinetics, increasing contact between His-tag and reactive groups of said carrier or membrane, by for instance the use of IDA or anti-His antibodies or increasing the

*considered  
full  
document*

hydrophobicity of the membrane, or shielding the rest of the biomol. from reaction by for instance increasing the hydrophobicity of said carrier or membrane or addn. of substrate or competitors or blocking otherwise reactive groups, or by choosing chem. reactions that have a high selectivity for histidine residues. A carrier can also be another biomol. The present invention thus also relates to a method that allows covalent crosslinking between identical or different biomols. When such biomols. have a natural tendency to interact with each other to form homo- or heterodimers, a strategy of increasing contact between the reactive groups (two His-tags or one His-tag and another reactive group) can be exploited. The present invention also relates to a method of providing a simultaneous and universal system for detection of biomols. through said His-tag.

- IC ICM G01N033-547  
ICS C07K017-06; C12N011-06; C07K017-00; C12N011-00
- CC 9-9 (Biochemical Methods)  
Section cross-reference(s): 6
- IT **Immunoassay**  
(enzyme-linked immunosorbent assay; methods for covalent immobilization of biomols. to a carrier by means of a histidine His-tag)
- IT 100-42-5, Styrene, biological studies 139-13-9, NTA 142-73-4, IDA  
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)  
(methods for covalent immobilization of biomols. to a carrier by means of a histidine His-tag)
- IT 108-31-6, Maleic anhydride, biological studies 111-30-8, Glutaraldehyde 616-02-4, Citraconic anhydride 816-39-7, 1,3-Dibromoacetone 25952-53-8, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride 109536-69-8, MMPP  
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
(methods for covalent immobilization of biomols. to a carrier by means of a histidine His-tag)
- IT 139-13-9, NTA  
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)  
(methods for covalent immobilization of biomols. to a carrier by means of a histidine His-tag)
- RN 139-13-9 HCAPLUS  
CN Glycine, N,N-bis(carboxymethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1997:794014 HCAPLUS  
DOCUMENT NUMBER: 128:59173  
TITLE: Determination of rheumatoid factor by latex agglutination test

INVENTOR(S): Kusuba, Toshio  
 PATENT ASSIGNEE(S): Sekisui Chemical Co., Ltd., Japan  
 SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.  
 CODEN: JKXXAF  
 DOCUMENT TYPE: Patent  
 LANGUAGE: Japanese  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

| PATENT NO.             | KIND  | DATE     | APPLICATION NO. | DATE     |
|------------------------|---|----------|-----------------|----------|
| JP 09318631            | A2  | 19971212 | JP 1996-137004  | 19960530 |
| PRIORITY APPLN. INFO.: |   |          | JP 1996-137004  | 19960530 |
| AB                     | Rheumatoid factor is detd. by treatment of a sample with human .gamma.-globulin-sensitized latex particles in the presence of .gtoreq.1 water-sol. compd. selected from trialkylamines, their salts, and quaternary ammonium salts and poly(vinylpyrrolidone) (I) and/or dextran, followed by measuring optical intensity. This method improves linearity of the relationship between the concns. of rheumatoid factor and the degree of agglutination. A 1st reagent (a phosphate buffer contg. BSA, NaCl, and I) and a 2nd reagent (a phosphate buffer contg. human .gamma.-globulin-sensitized polystyrene latex particles, choline chloride, BSA, and NaCl) were successively added to sample solns. of rheumatoid factor with various dilns., followed by measuring absorbance. Linearity of the calibration curve was good, while a control test using polyethylene glycol instead of I gave a sigmoid curve. |          |                 |          |
| IC                     | ICM G01N033-543   |          |                 |          |
|                        | ICS G01N033-531; G01N033-564  |          |                 |          |
| CC                     | 9-10 (Biochemical Methods)  |          |                 |          |
|                        | Section cross-reference(s): 14  |          |                 |          |
| IT                     | Rheumatoid factors  |          |                 |          |
|                        | RL: ANT (Analyte); ANST (Analytical study)  |          |                 |          |
|                        | (detn. of rheumatoid factor by <b>latex agglutination</b> test in presence of trialkylamines/quaternary ammonium salts and poly(vinylpyrrolidone)/dextran)  |          |                 |          |
| IT                     | Quaternary ammonium compounds, analysis   |          |                 |          |
|                        | RL: ARU (Analytical role, unclassified); ANST (Analytical study)  |          |                 |          |
|                        | (detn. of rheumatoid factor by <b>latex agglutination</b> test in presence of trialkylamines/quaternary ammonium salts and poly(vinylpyrrolidone)/dextran)  |          |                 |          |
| IT                     | <b>Immunoassay</b>  |          |                 |          |
|                        | (latex agglutination test; detn. of rheumatoid factor by <b>latex agglutination</b> test in presence of trialkylamines/quaternary ammonium salts and poly(vinylpyrrolidone)/dextran)  |          |                 |          |
| IT                     | <b>Amines, analysis</b>   |          |                 |          |
|                        | RL: ARU (Analytical role, unclassified); ANST (Analytical study)  |          |                 |          |
|                        | (tertiary; detn. of rheumatoid factor by <b>latex agglutination</b> test in presence of trialkylamines/quaternary ammonium salts and poly(vinylpyrrolidone)/dextran)  |          |                 |          |
| IT                     | Globulins, uses   |          |                 |          |
|                        | RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  |          |                 |          |
|                        | (.gamma.-, latex sensitized with human; detn. of rheumatoid factor by <b>latex agglutination</b> test in presence of trialkylamines/quaternary ammonium salts and poly(vinylpyrrolidone)/dextran)   |          |                 |          |
| IT                     | 60-31-1, Acetylcholine chloride 67-48-1, Choline chloride 9003-39-8,  |          |                 |          |

Poly(vinylpyrrolidone) 9004-54-0, Dextran, analysis  
 RL: ARU (Analytical role, unclassified); ANST (Analytical study)  
 (detn. of rheumatoid factor by **latex agglutination**  
 test in presence of trialkylamines/quaternary ammonium salts and  
 poly(vinylpyrrolidone)/dextran)

L29 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1997:526270 HCAPLUS

DOCUMENT NUMBER: 127:202547

TITLE: Prevention of nonspecific reaction in immunoassay with  
 masking agents, dispersants for filtration of feces,  
 and immunoassay of filtrated samples

INVENTOR(S): Kikuchi, Tatsunori

PATENT ASSIGNEE(S): Eiken Chemical Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE     | APPLICATION NO. | DATE     |
|------------------------|--|----------|-----------------|----------|
| JP 09203735            | A2   | 19970805 | JP 1996-31406   | 19960125 |
| PRIORITY APPLN. INFO.: |  |          | JP 1996-31406   | 19960125 |
| AB                     | <p>Nonspecific reaction in immunoassay caused by metal ions eluted from filter materials in filtration of samples is prevented by addn. of masking agents (e.g. complexons, phthalein complexons, oxines, and metal chelates) for metals in the samples. <u>Suspended fecal samples are filtrated in the presence of chelating agents and/or metal chelates for immunoassay.</u> Dispersants contg. chelating agents for filtration of suspended fecal samples are also claimed. The method prevents nonspecific reaction which is often obsd. in immunoassay for biol. samples after filtration with various filtration materials, e.g. paper filters, glass fiber filters, plastic filters, etc. Addn. of EDTA-2Na to HEPES buffer as a dispersant for feces samples suppressed nonspecific reaction in <b>latex agglutination</b> test for occult blood detection even after filtration of the dispersed samples with a glass fiber filter.</p> |          |                 |          |
| ICM                    | G01N033-72   |          |                 |          |
| ICS                    | G01N033-50; G01N033-543  |          |                 |          |
| CC                     | 9-10 (Biochemical Methods)   |          |                 |          |
| IT                     | <p><b>Immunoassay</b><br/>         (agglutination test; prevention of nonspecific reaction in immunoassay caused by metal ions eluted from filters for filtration of biol. samples by masking agents)</p>  |          |                 |          |
| IT                     | <p>139-13-9, Nitrilotriacetic acid 139-33-3 <b>150-25-4</b>,<br/>         N,N-Bis(2-hydroxyethyl)glycine 150-39-0, N-(2-Hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid <b>817-11-8</b>,<br/>         Nitrilotripropionic acid 4408-81-5, 1,2-Diaminopropane-N,N,N',N'-tetraacetic acid 6419-19-8, Nitrilotris(methylenephosphonic acid)<br/>         RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)<br/>         (prevention of nonspecific reaction in immunoassay caused by contact of biol. samples with filters by masking agents)</p>  |          |                 |          |
| IT                     | <p>60-00-4, Ethylenediamine-N,N,N',N'-tetraacetic acid, uses 67-43-6<br/> <b>93-62-9</b> 142-73-4, Iminodiacetic acid 482-54-2,<br/>         1,2-Cyclohexanediamine-N,N,N',N'-tetraacetic acid 1429-50-1,<br/>         Ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid) 1633-00-7</p>  |          |                 |          |

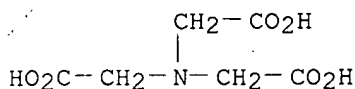
3148-72-9, 1,3-Diaminopropan-2-ol-N,N,N',N'-tetraacetic acid 5657-17-0,  
 Ethylenediamine-N,N'-diacetic acid 13288-40-9, Ethylenediamine-N,N'-  
 dipropionic acid 32701-19-2, Ethylenediaminediacetic acid dipropionic  
 acid

RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
 (prevention of nonspecific reaction in immunoassay caused by metal ions  
 eluted from filters for filtration of biol. samples by masking agents)

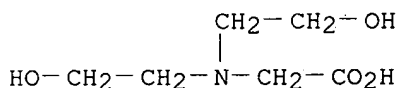
IT 139-13-9, Nitrilotriacetic acid 150-25-4,  
 N,N-Bis(2-hydroxyethyl)glycine 817-11-8, Nitrilotripropionic  
 acid

RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
 (prevention of nonspecific reaction in immunoassay caused by contact of  
 biol. samples with filters by masking agents)

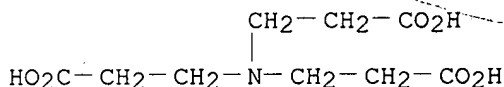
RN 139-13-9 HCAPLUS  
 CN Glycine, N,N-bis(carboxymethyl)- (9CI) (CA INDEX NAME)



RN 150-25-4 HCAPLUS  
 CN Glycine, N,N-bis(2-hydroxyethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)

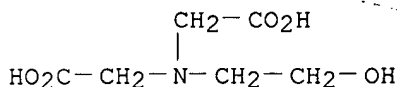


RN 817-11-8 HCAPLUS  
 CN .beta.-Alanine, N,N-bis(2-carboxyethyl)- (9CI) (CA INDEX NAME)



IT 93-62-9  
 RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
 (prevention of nonspecific reaction in immunoassay caused by metal ions  
 eluted from filters for filtration of biol. samples by masking agents)

RN 93-62-9 HCAPLUS  
 CN Glycine, N-(carboxymethyl)-N-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)



L29 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 1993:444697 HCAPLUS  
 DOCUMENT NUMBER: 119:44697

TITLE: Buffer and **latex agglutination**  
method for hemoglobin detection in feces  
INVENTOR(S): Tsuji, Takashi  
PATENT ASSIGNEE(S): Nitto Denko Corp, Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.  
CODEN: JKXXAF  
DOCUMENT TYPE: Patent  
LANGUAGE: Japanese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.             | KIND | DATE     | APPLICATION NO. | DATE     |
|------------------------|------|----------|-----------------|----------|
| JP 05099923            | A2   | 19930423 | JP 1991-292163  | 19911011 |
| PRIORITY APPLN. INFO.: |      |          | JP 1991-292163  | 19911011 |

AB Hb in feces is detected by **latex agglutination**  
immunoassay using anti-human Hb antibody-sensitized latex and a buffer  
contg. chelator (e.g. EDTA) to suspend the feces sample. The chelator in  
the buffer inhibited Hb denaturation and thus stabilized the test sample  
for a prolonged time.

IC ICM G01N033-531  
ICS G01N033-50; G01N033-53

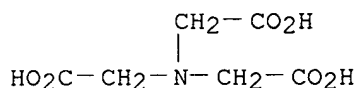
CC 9-10 (Biochemical Methods)

IT 60-00-4, EDTA, uses **139-13-9**, Nitrilotriacetic acid 139-33-3  
RL: USES (Uses)  
(buffer contg., for Hb detection in feces by agglutination immunoassay)

IT **139-13-9**, Nitrilotriacetic acid  
RL: USES (Uses)  
(buffer contg., for Hb detection in feces by agglutination immunoassay)

RN 139-13-9 HCAPLUS

CN Glycine, N,N-bis(carboxymethyl)- (9CI) (CA INDEX NAME)



L29 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1989:530314 HCAPLUS  
DOCUMENT NUMBER: 111:130314  
TITLE: Determination of human C-reactive protein by a  
**latex agglutination test**  
INVENTOR(S): Tanno, Kazunobu; Iijima, Hiromi; Kawagoe, Kiyotaka  
PATENT ASSIGNEE(S): Hitachi Chemical Co., Ltd., Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.  
CODEN: JKXXAF  
DOCUMENT TYPE: Patent  
LANGUAGE: Japanese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|-------------|------|----------|-----------------|----------|
| JP 63298061 | A2   | 19881205 | JP 1987-133076  | 19870528 |
| JP 07107534 | B4   | 19951115 |                 |          |

PRIORITY APPLN. INFO.: JP 1987-133076 19870528  
AB A sample is mixed with insol. carriers sensitized with anti-human C-reactive protein antibody and treated with a trialkylamine or its (quaternary ammonium) salts for agglutination; the optical d. is measured for human C-reactive protein detn. A sample was dild. with a soln. contg. choline chloride, NaCl and bovine serum albumin (in phosphate buffer, pH 6.5) and treated with antibody-sensitized polystyrene latex particles, and the reaction mixt. was measured at 570 nm for human C-reactive protein detn.  
IC ICM G01N033-53  
ICS G01N033-543  
CC 9-10 (Biochemical Methods)  
IT Proteins, specific or class  
RL: ANT (Analyte); ANST (Analytical study)  
(C-reactive, detn. of, by **latex agglutination** test, trialkylamines in, optical d. measurement in relation to)  
IT **Amines, uses and miscellaneous**  
RL: ANST (Analytical study)  
(**tertiary**, in C-reactive protein detn. by agglutination test, optical d. measurement in relation to)

L29 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1988:201348 HCAPLUS  
DOCUMENT NUMBER: 108:201348  
TITLE: Reagents for quantitative determination of C-reactive protein  
INVENTOR(S): Tanno, Kazunobu; Iijima, Hiromi; Kawagoe, Kyotaka  
PATENT ASSIGNEE(S): Hitachi Chemical Co., Ltd., Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.  
CODEN: JKXXAF  
DOCUMENT TYPE: Patent  
LANGUAGE: Japanese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|-------------|------|----------|-----------------|----------|
| JP 62218866 | A2   | 19870926 | JP 1986-62819   | 19860320 |
| JP 05040868 | B4   | 19930621 |                 |          |

PRIORITY APPLN. INFO.: JP 1986-62819 19860320  
AB Reagents for quant. detn. of C-reactive protein by **latex agglutination** tests consist of anti-human C-reactive protein antibody-sensitized insol. carriers and water-sol. compds. selected from trialkylamines, their salts, and quaternary ammonium salts. A sample was dild. with pH 6.5 phosphate buffer contg. choline chloride, NaCl and bovine serum albumin, and incubated with a reagent contg. 0.4% sensitized polystyrene latex particles at 37.degree., and the absorbance at 570 nm was monitored for C-reactive protein quantitation.  
IC ICM G01N033-543  
ICS G01N033-53  
CC 9-10 (Biochemical Methods)  
IT **Amines, compounds**  
RL: ANST (Analytical study)  
(**tertiary**, C-reactive protein detn. by agglutination test with reagents contg., enhanced sensitivity in relation to)

L29 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:201347 HCAPLUS  
DOCUMENT NUMBER: 108:201347  
TITLE: Rheumatoid factor determination by **latex agglutination** tests  
INVENTOR(S): Tanno, Kazunobu; Iijima, Hiromi  
PATENT ASSIGNEE(S): Hitachi Chemical Co., Ltd., Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.  
CODEN: JKXXAF  
DOCUMENT TYPE: Patent  
LANGUAGE: Japanese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|-------------|------|----------|-----------------|----------|
| JP 62218865 | A2   | 19870926 | JP 1986-62818   | 19860320 |
| JP 06068492 | B4   | 19940831 |                 |          |

PRIORITY APPLN. INFO.: JP 1986-62818 19860320

AB A sample contg. rheumatoid factor is mixed with human .gamma.-globulin-sensitized insol. carriers and .gtoreq.1 water-sol. compds. selected from polyethylene glycol, trialkylamine and their salts for agglutination, and the optical d. is measured for the quantitation of rheumatoid factor. A serum sample was dild. with 0.05M phosphate buffer contg. 0.9% polyethylene glycol and incubated with a reagent contg. human .gamma.-globulin-sensitized polystyrene latex at 37.degree. and measured at 570 nm for rheumatoid factor detn.

IC ICM G01N033-543  
ICS G01N033-564

CC 9-10 (Biochemical Methods)

IT **Amines, compounds**  
RL: ANST (Analytical study)  
(**tertiary**, rheumatoid factor detn. by agglutination test with reagents contg., enhanced sensitivity in relation to)

L29 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:201346 HCAPLUS  
DOCUMENT NUMBER: 108:201346  
TITLE: Quantitative determination of human C-reactive protein by **latex agglutination** tests  
INVENTOR(S): Tanno, Kazunobu; Iijima, Hiromi; Kawagoe, Kyotaka  
PATENT ASSIGNEE(S): Hitachi Chemical Co., Ltd., Japan  
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.  
CODEN: JKXXAF  
DOCUMENT TYPE: Patent  
LANGUAGE: Japanese  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|-------------|------|----------|-----------------|----------|
| JP 62218864 | A2   | 19870926 | JP 1986-62817   | 19860320 |
| JP 05040867 | B4   | 19930621 |                 |          |

PRIORITY APPLN. INFO.: JP 1986-62817 19860320

AB A sample contg. human C-reactive protein is mixed with anti-C-reactive protein antibody-sensitized insol. carriers and water-sol. compds. selected from trialkylamine or salts for agglutination, and the optical d. is measured for quantitation. A sample was dild. with 0.05M phosphate



buffer contg. choline chloride, NaCl and bovine serum albumin, and incubated with a reagent contg. sensitized polystyrene latex particles at 37.degree., and the absorbance at 570 nm was measured for C-reactive protein detn.

IC ICM G01N033-543

ICS G01N033-53; G01N033-557

CC 9-10 (Biochemical Methods)

IT **Amines, compounds**

RL: ANST (Analytical study)

(**tertiary**, C-reactive protein detn. by agglutination test with reagents contg., enhanced sensitivity in relation to)

L29 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1987:172483 HCAPLUS

DOCUMENT NUMBER: 106:172483

TITLE: Aminocarboxylates and aminosulfonates as stabilizers for agglutination test reagents

INVENTOR(S): Kihara, Yasuo; Kawasaki, Takashi; Mori, Kenjiro; Ushiyama, Keiichi

PATENT ASSIGNEE(S): Nitto Electric Industrial Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

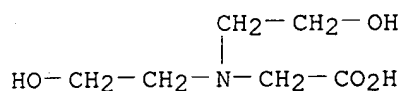
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

|                        | PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|------------------------|--|------|----------|-----------------|----------|
|                        | JP 61274261  | A2   | 19861204 | JP 1985-118586  | 19850530 |
| PRIORITY APPLN. INFO.: |  |      |          | JP 1985-118586  | 19850530 |
| AB                     | The aminocarboxylates <u>A3-mN(BCO2H)</u> [A = H, (un)substituted alkyl; B = (un)substituted alkylene; m = 1 or 2; when m = 2, A .noteq. H] or the aminosulfonates XYNZSO3H [X, Y = H, (un)satd. alkyl, cycloalkyl, cycloamino; Z = (un)satd. alkylene; X = Y .noteq. H] are added to an aq. dispersion contg. sensitized, dispersible polymer particles (latex) to increase the reagent stability and agglutination test specificity. |      |          |                 |          |
| IC                     | ICM G01N033-545  |      |          |                 |          |
| ICA                    | A61K039-00   |      |          |                 |          |
| CC                     | 9-10 (Biochemical Methods)   |      |          |                 |          |
| IT                     | <b>Immunochemical analysis</b><br>( <b>agglutination test</b> , aminocarboxylates or aminosulfonates with latex reagents contg. sensitized and water-dispersible polymer particles for, to increase stability and specificity)   |      |          |                 |          |
| IT                     | Sulfonic acids, biological studies<br>RL: ANST (Analytical study)<br>(amino, <b>agglutination test latex</b> reagents contg., to increase stability and specificity)   |      |          |                 |          |
| IT                     | Carboxylic acids, biological studies<br>RL: ANST (Analytical study)<br>(iminodi-, <b>agglutination test latex</b> reagents contg., to increase stability and specificity)  |      |          |                 |          |
| IT                     | Amino acids, biological studies<br>RL: ANST (Analytical study)<br>(.omega.-, <b>agglutination test latex</b> reagents contg., to increase stability and specificity)   |      |          |                 |          |

IT 103-47-9 150-25-4 1132-61-2 1135-40-6 4432-31-9  
5625-37-6 5704-04-1 7365-82-4 10191-18-1 26239-55-4 68189-43-5  
68399-77-9 68399-80-4 107900-92-5 107900-93-6 107900-94-7  
RL: ANST (Analytical study)  
(agglutination test latex reagents contg., to  
increase stability and specificity)  
IT 150-25-4  
RL: ANST (Analytical study)  
(agglutination test latex reagents contg., to  
increase stability and specificity)  
RN 150-25-4 HCAPLUS  
CN Glycine, N,N-bis(2-hydroxyethyl)- (6CI, 8CI, 9CI) (CA INDEX NAME)



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L4

STR

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      4
      G1
      }
G1~N~G1
1  2  3

      Ak~G2      Ak~O~Ak~G2      O~Ak      S~Ak
      @5  6      @7  8  9  10      @11 12      @13 14

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O=C~O
15 @16 17

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O=C~O~Ak
18 @19 20 21

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O=C~N~Ak
22 @23 24 25

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VAR G1=5/7

VAR G2=OH/11/13/16/19/23

NODE ATTRIBUTES:

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CONNECT IS E3 RC AT 2
CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 7
CONNECT IS E2 RC AT 9
CONNECT IS E1 RC AT 12
CONNECT IS E2 RC AT 13
CONNECT IS E1 RC AT 14
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CONNECT IS E1 RC AT 25
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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GRAPH ATTRIBUTES:

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

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STEREO ATTRIBUTES: NONE

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L6      405652 SEA FILE=REGISTRY ABB=ON PLU=ON (((N AND C AND O AND H)/ELS
AND 4/ELC.SUB) OR ((N AND C AND S AND H)/ELS AND 4/ELC.SUB) OR
((N AND C AND O AND S AND H)/ELS AND 5/ELC.SUB)) AND NC=1 NOT
RSD/FA

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L11      651 SEA FILE=REGISTRY SUB=L6 SSS FUL L4

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L37      2145 SEA L11

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L38      19124 SEA TERT?(2A) AMINE

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L39      101 SEA (L37 OR L38) AND (CDI OR CARBODIIMID? OR (PARTICL? OR
LATEX) (5A) (AGGLUT? OR FIX?))

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L40      9 SEA L39 AND (IMMUNO? OR ASSAY?)

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L41      9 DUP REM L40 (0 DUPLICATES REMOVED)

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L41 ANSWER 1 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-646011 [61] WPIX

DOC. NO. CPI: C2003-176727

TITLE: New tyrosyl piperazine derivatives are purinergic P2X7  
receptor modulators, useful for treating e.g. rheumatoid  
arthritis, cancer, lupus erythematosus.

DERWENT CLASS: B02 B03  
 INVENTOR(S): BARALDI, P G; BOREA, P A  
 PATENT ASSIGNEE(S): (BARA-I) BARALDI P G; (BORE-I) BOREA P A; (KING-N) KING  
 PHARM RES & DEV INC  
 COUNTRY COUNT: 100  
 PATENT INFORMATION:

| PATENT NO  | KIND | DATE     | WEEK      | LA | PG |
|--|------|----------|-----------|----|----|
| WO 2003059353  | A1   | 20030724 | (200361)* | EN | 34 |
| RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU<br>MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW  |      |          |           |    |    |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK<br>DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR<br>KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT<br>RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW |      |          |           |    |    |
| US 2003181452  | A1   | 20030925 | (200364)  |    |    |

## APPLICATION DETAILS:

| PATENT NO     | KIND           | APPLICATION     | DATE     |
|---------------|----------------|-----------------|----------|
| WO 2003059353 | A1             | WO 2002-US41385 | 20021223 |
| US 2003181452 | A1 Provisional | US 2001-342977P | 20011221 |
|               |                | US 2002-329094  | 20021223 |

PRIORITY APPLN. INFO: US 2001-342977P 20011221; US 2002-329094  
 20021223

AN 2003-646011 [61] WPIX

AB WO2003059353 A UPAB: 20030923

NOVELTY - Tyrosyl piperazine derivatives (I)-(IV) are new.

DETAILED DESCRIPTION - Tyrosyl piperazine derivatives of formula  
 (I)-(IV) and their salts are new.

R1, R2 = 1-4C alkyl or 1-4C alkoxy (both optionally substituted), H,  
 1-4C acyl, halo, NO2, NH2 or (di)alkylamino;

R3-R8 = CH or N;

R9 = H or Me;

R10 = CO or (CH2)n;

n, n' = 0-4;

R11, R12 = N or CH;

X1, X2 = H, deuterium, tritium or halo;

X3 = N or CH;

R1a, R2a = H, 1-4C alkyl, 1-4C alkoxy, 1-4C acyl, halo, CN, NO2, NH2,  
 or (di)alkylamino; and

R1b, R2b = H, 1-4C alkyl, 1-4C alkoxy, halo, CN, NO2 or NH2;

provided that when n' = 0, R1b and R2b are not both H.

ACTIVITY - Antiinflammatory; **Immunosuppressive**;  
 Antirheumatic; Antiarthritic; Tuberculostatic; Antiinfertility;  
 Dermatological; Cytostatic; Vulnerary.

MECHANISM OF ACTION - Purinergic P2X7 Receptor Modulator.

Adenosine triphosphate (ATP) dependent increases in plasma membrane  
 permeability were measured with extracellular fluorescent tracer ethidium  
 bromide. For ethidium bromide uptake cells were incubated in a  
 thermostat-controlled fluorometer cuvette (37 deg. C) for 20 minutes in  
 the dark at concentration of 1000000 cells/ml in the presence of ethidium  
 bromide (20 mM) and challenged with ATP (1 mM). Cell suspension was

incubated with 1-((S)-N,O-bis(isoquinolinesulfonyl)-N-methyl-tyrosyl)-4-(4-fluorophenyl)piperazine (IVa) (25-5000 nM) for 5 minutes at 37 deg. C before fluorimetric analysis in a stirred cuvette at 37 deg. C. Fluorescence changes were monitored at the wavelength pair 360/580 nm. After several washing to remove extracellular dye, cells were analyzed with an inverted fluorescence microscope. (IVa) Inhibited ATP dependent increases in plasma membrane permeability with an IC50 of 1.33 nM.

USE - For inducing apoptosis in neoplastic cell and in treating medical conditions (e.g. inflammatory disease, disease of immune system, rheumatoid arthritis, tuberculosis, sterility, inflammatory bowel disease, lupus erythematosus, organ transplant, cancer and wound) in a human (claimed).

Dwg.0/4

L41 ANSWER 2 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-692243 [66] WPIX

DOC. NO. CPI: C2003-190361

TITLE: New benzamide derivative or its salts, useful for preventing and treating diseases such as osteoporosis, diabetes, hyperlipidemia and arteriosclerosis, has peroxisome proliferator activated receptor modulator activity.

DERWENT CLASS: B05

PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD

COUNTRY COUNT: 1

PATENT INFORMATION:

| PATENT NO     | KIND | DATE     | WEEK      | LA | PG |
|---------------|------|----------|-----------|----|----|
| JP 2003128639 | A    | 20030508 | (200366)* |    | 49 |

APPLICATION DETAILS:

| PATENT NO     | KIND | APPLICATION    | DATE     |
|---------------|------|----------------|----------|
| JP 2003128639 | A    | JP 2001-327197 | 20011025 |

PRIORITY APPLN. INFO: JP 2001-327197 20011025

AN 2003-692243 [66] WPIX

AB JP2003128639 A UPAB: 20031014

NOVELTY - Novel benzamide derivatives (I) and their salts.

DETAILED DESCRIPTION - New benzamide derivatives of formula (I), and their salts.

A = H, amino group, 1-12C alkylamino, 2-8C alkanoyl amino, 1-6C alkoxy, hydroxy, mercapto, carboxy, 2-7C alkyloxycarbonyl, sulfonyl, 1-6C alkylsulfonyl, 1-6C alkyl or heterocyclyl (substituted with one or more amino or hydroxy);

Alk = 1-6C alkylene group;

B = single bond, aryl, cycloalkyl or heterocyclyl (all optionally substituted with (alpha) 1-6C alkyl, nitro, cyano, carboxy, 2-7C alkyloxycarbonyl, 3-15C alkyloxycarbonylalkyl or amino (optionally substituted with 3-6C alkenyl, halo, 1-6C haloalkyloxy, 1-6C alkoxy, 1-6C alkylthio, amidino-aminosulfonyl or phenyl);

R1 = H, 1-6C alkyl or aralkyl; and

X1,X2 = single bond, O, S, CO, N, SO2N, NSO2, CONH or NHCO.

ACTIVITY - Osteopathic; Antidiabetic; Anorectic;

Antiartherosclerotic; Antilipemic; Antiinflammatory; **Immunosuppressive**; Cytostatic; Hepatotrophic; Vasotropic; Cardiant; Nootropic; Neuroprotective; Hypotensive; Nephrotropic. 8-week-old Syrian golden hamster male rats were ingested with a diet containing 0.3% (weight/weight) of N-(2-(4-(phenyl sulfonyl amino) phenyl) ethyl)-(2-chloro-5-nitrophenyl) carboxamide for 1 week. After 1 week, the total high density lipoprotein cholesterol (HDL-TC) and free HDL cholesterol (HDL-FC), were evaluated in HDL fraction using HDL cholesterol precipitate test reagent. The HDL-TC and HDL-FC were found to be 107.4% and 135.2%, respectively. The results concluded the compound exhibited remarkable antiatherosclerotic effect.

**MECHANISM OF ACTION** - PPAR-Agonist-Gamma; Leptin-Agonist. Fat tissues extracted from wister imamichi male rat (6-week-old) was mixed with of Hanks liquid 1 ml containing of collagenase (10 mg), shaken for 50 minutes and incubated at 90 rpm and 37 deg. C. 20 ml of Hanks liquid was then mixed, filtered and centrifuged for 1 minute at 1000 rpm. Fat cell suspension (60 ml) was then mixed with of culture medium (100 micro l) and of N-(1-phenyl ethyl)-(2-chloro-5-nitrophenyl) carboxamide (1 micro l) and incubated for 1 hour or more at 30 deg. C. The leptin concentration was measured by enzyme linked **immunosorbant assay** (ELISA) method using rat leptin measurement kit-IBL. The leptin production was 109.4%, thus demonstrating that the test compound exhibited excellent leptin-agonist effect.

**USE** - For preventing and treating osteoporosis, diabetes, obesity, arteriosclerosis, hyperlipidemia, abnormality in lipid metabolism, pancreatitis, autoimmune diseases, hyperuricemia, leukemia, abnormality in liver function, ischemia, cancer, inflammation, Basedow's disease, cardiac disease, Alzheimers disease, eating disorders, hypertension and renal diseases.

**ADVANTAGE** - The new benzamide derivatives having excellent peroxisome proliferator activated receptor-( gamma ) modulator activity is effectively used in preventing and treating osteoporosis. The benzamide derivative or its salts can be manufacture easily and effectively with improved yield.

Dwg.0/3

L41 ANSWER 3 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN  
 ACCESSION NUMBER: 2003-723291 [69] WPIX  
 DOC. NO. NON-CPI: N2003-578338  
 DOC. NO. CPI: C2003-199176  
 TITLE: **Immunoassay** reagent comprising particles with a surface activated by a **carbodiimide** and linked to a binding agent, and a **tertiary amine** compound useful for preventing non-specific interactions in **particle agglutination immunoassays**.  
 DERWENT CLASS: B04 D16 S03  
 INVENTOR(S): LAWRENCE, C C; SHANAFELT, A B  
 PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) ROCHE DIAGNOSTICS GMBH; (LAWR-I) LAWRENCE C C; (SHAN-I) SHANAFELT A B  
 COUNTRY COUNT: 33  
 PATENT INFORMATION:

| PATENT NO  | KIND | DATE     | WEEK      | LA | PG |
|------------|------|----------|-----------|----|----|
| EP 1321770 | A2   | 20030625 | (200369)* | EN | 13 |

R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC  
 MK NL PT RO SE SI SK TR  
 CA 2414704 A1 20030618 (200369) EN  
 JP 2003207512 A 20030725 (200369) 36  
 US 2003138974 A1 20030724 (200369)

## APPLICATION DETAILS:

| PATENT NO     | KIND | APPLICATION     | DATE     |
|---------------|------|-----------------|----------|
| EP 1321770    | A2   | EP 2002-27992   | 20021214 |
| CA 2414704    | A1   | CA 2002-2414704 | 20021217 |
| JP 2003207512 | A    | JP 2002-363686  | 20021216 |
| US 2003138974 | A1   | US 2001-25378   | 20011218 |

PRIORITY APPLN. INFO: US 2001-25378 20011218

AN 2003-723291 [69] WPIX

AB EP 1321770 A UPAB: 20031027

NOVELTY - A reagent for use in **immunoassays** comprising multiple particles, each having a surface activated by a **carbodiimide**, a binding agent linked to the surface through a covalent bond, and a **tertiary amine** compound, is new.

DETAILED DESCRIPTION - A reagent (R) for use in **immunoassays**, comprises multiple particles, each having a surface activated by a **carbodiimide**, a binding agent linked to the surface through a covalent bond, and a **tertiary amine** compound of formula (I).

$N(R_1-X)(R_2-Y)(R_3-Z)$  (I),

where  $R_1$ ,  $R_2$  and  $R_3$  are independently chosen from alkyl and alkyl ether; and

$X$ ,  $Y$ , and  $Z$  are independently chosen from  $-OH$ ,  $-O-R_4$ ,  $-S-R_4$ ,  $-C(=O)-OH$ ,  $-C(=O)-OR_4$ , and  $-C(=O)-NHR_4$ , where  $R_4$  is alkyl.

INDEPENDENT CLAIMS are also included for:

(1) a test kit comprising (R);  
 (2) an **immunoassay** method (M1), in which a sample suspected of containing an analyte is combined with (R), where the improvement comprises the addition of the **tertiary amine** of formula (I); and

(3) use of a **tertiary amine** compound of formula (I) in **particle-based agglutination immunoassay** to prevent non-specific interactions.

USE - (R) is useful in **particle-based agglutination immunoassays**, the **tertiary amine** helping to prevent non-specific interactions (claimed).

ADVANTAGE - (R) improves the accuracy of **particle-based agglutination immunoassays** by reducing or eliminating non-specific interactions.

DESCRIPTION OF DRAWING(S) - The figure shows the graph of the dependence of the absorbance at 468 nm due to bound orange 7 dye as a function of particle concentration.

Dwg.1/4

L41 ANSWER 4 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2002-519057 [55] WPIX

DOC. NO. NON-CPI: N2002-410923

DOC. NO. CPI: C2002-146734

TITLE: New biodegradable, blood-compatible biopolymer comprising crosslinked polyubiquitin, forming hydrogels or matrices useful e.g. as wound dressings, drug delivery vehicles or enzyme biosensors.

DERWENT CLASS: A96 B04 P34

INVENTOR(S): BOSSE, M

PATENT ASSIGNEE(S): (VIRI-N) VIRIDIS BIOTECH INC; (BOSS-I) BOSSE M

COUNTRY COUNT: 97

PATENT INFORMATION:

| PATENT NO  | KIND | DATE     | WEEK      | LA | PG |
|--|------|----------|-----------|----|----|
| WO 2001091814  | A2   | 20011206 | (200255)* | EN | 75 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ<br>NL OA PT SD SE SL SZ TR TZ UG ZW  |      |          |           |    |    |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK<br>DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR<br>KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU<br>SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW |      |          |           |    |    |
| AU 2001067181  | A    | 20011211 | (200255)  |    |    |
| EP 1284992   | A2   | 20030226 | (200319)  | EN |    |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT<br>RO SE SI TR  |      |          |           |    |    |
| US 2003114724  | A1   | 20030619 | (200341)  |    |    |

## APPLICATION DETAILS:

| PATENT NO     | KIND | APPLICATION    | DATE     |
|---------------|------|----------------|----------|
| WO 2001091814 | A2   | WO 2001-CA784  | 20010529 |
| AU 2001067181 | A    | AU 2001-67181  | 20010529 |
| EP 1284992    | A2   | EP 2001-944783 | 20010529 |
|               |      | WO 2001-CA784  | 20010529 |
| US 2003114724 | A1   | WO 2001-CA784  | 20010529 |
|               |      | US 2002-275985 | 20021120 |

## FILING DETAILS:

| PATENT NO     | KIND        | PATENT NO     |
|---------------|-------------|---------------|
| AU 2001067181 | A Based on  | WO 2001091814 |
| EP 1284992    | A2 Based on | WO 2001091814 |

PRIORITY APPLN. INFO: US 2000-207325P 20000530; US 2002-275985  
20021120

AN 2002-519057 [55] WPIX

AB WO 200191814 A UPAB: 20030919

NOVELTY - A novel biopolymer (A) comprises a 3-dimensionally crosslinked mixture of ubiquitin (I) (a small protein having a sequence of 76 amino acids given in the specification) and at least one crosslinking agent (II).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(i) preparation of (A);

(ii) a biopolymer comprising (I), a solvent for (I) and at least one (II); and

(iii) the use of (I) in the preparation of (A).

ACTIVITY - Hemostatic; vulnerary.



MECHANISM OF ACTION - None given in the source material.

USE - (A) form hydrogels or matrices useful as wound dressings, biodegradable vehicles for oral, parenteral or topical drug delivery, enzyme biosensors for detection of nucleic or peptide molecules, in situ hybridization systems (e.g. for use in diagnostic assays), in vitro model systems for research, hemostatic agents, prostheses or implants (possibly containing cell cultures).

ADVANTAGE - (A) are biodegraded to non-toxic, endogenous materials; have good blood compatibility and low immunogenicity and can be prepared with a wide range of controllable properties (e.g. hydrophilicity, charge, degree of crosslinking, drug uptake and degradation/release kinetics).

Dwg.0/18

L41 ANSWER 5 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2002-055454 [07] WPIX

DOC. NO. CPI: C2002-015870

TITLE: Purification compound for making pure immunoglobulins for therapeutic and diagnostic applications, includes non-peptidic ligand attached to support matrix.

DERWENT CLASS: A11 A25 A96 B04

INVENTOR(S): GRIFFIN, M; SCARPA, I; STIPANOVIC, B

PATENT ASSIGNEE(S): (ACCU-N) ACCURATE POLYMERS INC; (ACCU-N) ACCURATE POLYMERS LTD; (GRIF-I) GRIFFIN M; (SCAR-I) SCARPA I; (STIP-I) STIPANOVIC B

COUNTRY COUNT: 96

PATENT INFORMATION:

| PATENT NO   | KIND | DATE     | WEEK      | LA | PG |
|---|------|----------|-----------|----|----|
| WO 2001083515   | A2   | 20011108 | (200207)* | EN | 23 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ |      |          |           |    |    |
| NL OA PT SD SE SL SZ TR TZ UG ZW                                      |      |          |           |    |    |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  |      |          |           |    |    |
| DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ     |      |          |           |    |    |
| LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD     |      |          |           |    |    |
| SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW                    |      |          |           |    |    |
| US 2001045384   | A1   | 20011129 | (200207)  |    |    |
| AU 2001059293   | A    | 20011112 | (200222)  |    |    |
| EP 1276557  | A2   | 20030122 | (200308)  | EN |    |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  |      |          |           |    |    |
| RO SE SI TR   |      |          |           |    |    |
| US 6572767  | B2   | 20030603 | (200339)  |    |    |

APPLICATION DETAILS:

| PATENT NO     | KIND           | APPLICATION     | DATE     |
|---------------|----------------|-----------------|----------|
| WO 2001083515 | A2             | WO 2001-US13970 | 20010430 |
| US 2001045384 | A1 Provisional | US 2000-200591P | 20000428 |
|               |                | US 2001-846471  | 20010430 |
| AU 2001059293 | A              | AU 2001-59293   | 20010430 |
| EP 1276557    | A2             | EP 2001-932794  | 20010430 |
|               |                | WO 2001-US13970 | 20010430 |
| US 6572767    | B2 Provisional | US 2000-200591P | 20000428 |
|               |                | US 2001-846471  | 20010430 |

## FILING DETAILS:

| PATENT NO     | KIND        | PATENT NO     |
|---------------|-------------|---------------|
| AU 2001059293 | A Based on  | WO 2001083515 |
| EP 1276557    | A2 Based on | WO 2001083515 |

PRIORITY APPLN. INFO: US 2000-200591P 20000428; US 2001-846471  
20010430

AN 2002-055454 [07] WPIX

AB WO 200183515 A UPAB: 20020130

NOVELTY - A purification compound comprises a support matrix and a non-peptidic ligand.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for (A) a method of manufacturing the ligand compounds of formulae (I), (II), (III), and (IV); and (B) a purification method comprising providing the specified support matrix having a non-peptidic ligand, introducing the support matrix to a solution containing a target compound, allowing for an interaction to occur between the ligand and the target compound, washing the beads having a ligand to the target compound so that the target compound is eluted from the solution. The support matrix is reusable. Formula (I) is manufactured by reacting 2-anilino-4,6-dichloro-s-triazine with a molecular super-structure having a terminal hydrazide functional group. Formula (II) is manufactured by reacting a (4' hydroxy)phenetyalmido-1-carboxy-anilido-3-carboxyphenyl-5-amine with a terminal, activated ester functional group, or reacting a 5-amino bisamide with a carbonyl group. Formula (III) is manufactured by reacting a 5-amino bisamide with a carbonyl group, or reacting a (a(4, hydroxy)phenetyalmido-1-carboxy-anilido-3-carboxyphenyl-5-amine with a terminal **tertiary** dicarboxy-ethyl **amine** in the presence of a peptide-coupling agent. Formula (IV) is manufactured by reacting a primary amino group on a spacer arm with a triepoxy compound to form a terminal diepoxy compound, and reacting the terminal diepoxy compound with a mercaptoheterocyclic compound.

USE - For making pure **immunoglobulins** for therapeutic and diagnostic applications.

ADVANTAGE - The large-scale purification of bio-molecules and, in particular, **immunoglobulines**, is accomplished by using a cellulose bead attached to small, non-peptidic compounds which display a high affinity and selectivity for the biomolecule to be purified. The beads with the attached ligands of formulae (I-IV) also possess a high chemical stability under rigors of recycling and sterilization.

Dwg.0/0

L41 ANSWER 6 OF 9 WPIX COPYRIGHT 2003 THOMSON.DERWENT on STN

ACCESSION NUMBER: 1999-215021 [18] WPIX

DOC. NO. CPI: C1999-063354

TITLE: Preparation of 5,6-dihydro-4-hydroxy-2H-pyran-2-one derivatives useful as intermediates for antiviral agent.

DERWENT CLASS: B03

INVENTOR(S): GAGE, J R; HEWITT, B D; KELLY, R C

PATENT ASSIGNEE(S): (PHAA) PHARMACIA & UPJOHN CO

COUNTRY COUNT: 83

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|-----------|------|------|------|----|----|
|-----------|------|------|------|----|----|

-----  
 WO 9912919 A1 19990318 (199918)\* EN 45  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SZ UG ZW  
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
 GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG  
 US UZ VN YU ZW  
 AU 9892965 A 19990329 (199932)  
 FI 2000000553 A 20000310 (200028)  
 NO 2000001274 A 20000510 (200034)  
 EP 1015441 A1 20000705 (200035) EN  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
 RO SE SI  
 US 6077963 A 20000620 (200035)  
 CZ 2000000804 A3 20000816 (200048)  
 SK 2000000226 A3 20001009 (200056)  
 CN 1268947 A 20001004 (200067)  
 HU 2000003593 A2 20010228 (200121)  
 US 6265604 B1 20010724 (200146)  
 MX 2000002411 A1 20001001 (200158)  
 KR 2001023864 A 20010326 (200161)  
 JP 2001515895 W 20010925 (200170) 53  
 AU 743496 B 20020124 (200221)  
 NZ 503338 A 20020301 (200224)  
 NZ 516325 A 20021220 (200309)

## APPLICATION DETAILS:

| PATENT NO     | KIND           | APPLICATION     | DATE     |
|---------------|----------------|-----------------|----------|
| WO 9912919    | A1             | WO 1998-US17993 | 19980903 |
| AU 9892965    | A              | AU 1998-92965   | 19980903 |
| FI 2000000553 | A              | WO 1998-US17993 | 19980903 |
|               |                | FI 2000-553     | 20000310 |
| NO 2000001274 | A              | WO 1998-US17993 | 19980903 |
|               |                | NO 2000-1274    | 20000310 |
| EP 1015441    | A1             | EP 1998-945806  | 19980903 |
|               |                | WO 1998-US17993 | 19980903 |
| US 6077963    | A Provisional  | US 1997-58618P  | 19970911 |
|               | Cont of        | US 1998-146406  | 19980903 |
|               |                | US 1998-213887  | 19981217 |
| CZ 2000000804 | A3             | WO 1998-US17993 | 19980903 |
|               |                | CZ 2000-804     | 19980903 |
| SK 2000000226 | A3             | WO 1998-US17993 | 19980903 |
|               |                | SK 2000-226     | 19980903 |
| CN 1268947    | A              | CN 1998-808711  | 19980903 |
| HU 2000003593 | A2             | WO 1998-US17993 | 19980903 |
|               |                | HU 2000-3593    | 19980903 |
| US 6265604    | B1 Provisional | US 1997-58618P  | 19970911 |
|               | Cont of        | US 1998-146406  | 19980903 |
|               | Div ex         | US 1998-213887  | 19981217 |
|               |                | US 2000-514087  | 20000228 |
| MX 2000002411 | A1             | MX 2000-2411    | 20000309 |
| KR 2001023864 | A              | KR 2000-702546  | 20000310 |
| JP 2001515895 | W              | WO 1998-US17993 | 19980903 |
|               |                | JP 2000-510727  | 19980903 |

|           |   |        |                 |          |
|-----------|---|--------|-----------------|----------|
| AU 743496 | B |        | AU 1998-92965   | 19980903 |
| NZ 503338 | A |        | NZ 1998-503338  | 19980903 |
|           |   |        | WO 1998-US17993 | 19980903 |
| NZ 516325 | A | Div ex | NZ 1998-503338  | 19980903 |
|           |   |        | NZ 1998-516325  | 19980903 |

## FILING DETAILS:

| PATENT NO     | KIND |                | PATENT NO  |
|---------------|------|----------------|------------|
| AU 9892965    | A    | Based on       | WO 9912919 |
| EP 1015441    | A1   | Based on       | WO 9912919 |
| CZ 2000000804 | A3   | Based on       | WO 9912919 |
| HU 2000003593 | A2   | Based on       | WO 9912919 |
| JP 2001515895 | W    | Based on       | WO 9912919 |
| AU 743496     | B    | Previous Publ. | AU 9892965 |
|               |      | Based on       | WO 9912919 |
| NZ 503338     | A    | Div in         | NZ 516325  |
|               |      | Based on       | WO 9912919 |
| NZ 516325     | A    | Div ex         | NZ 503338  |

PRIORITY APPLN. INFO: US 1997-58618P 19970911; US 1998-146406  
 19980903; US 1998-213887 19981217; US  
 2000-514087 20000228

AN 1999-215021 [18] WPIX

AB WO 9912919 A UPAB: 20011203

NOVELTY - 5,6-Dihydro-4-hydroxy-2H-pyran-2-one derivatives (CVI) are prepared by reacting the activated form of a 3-hydroxypropanoic acid derivative (CIV') with a malonate monoester and a divalent metal then contacting with an acid followed by a base (B2) in the presence of a 1-4C alcohol, tetrahydrofuran or dimethylformamide.

DETAILED DESCRIPTION - Preparation of 5,6-dihydro-4-hydroxy-2H-pyran-2-one derivatives of formula (CVI) comprises:

- (a) contacting a 3-hydroxypropanoate salt of formula (CIV) with an acid (A1);
- (b) extracting the free acid (CIV') formed;
- (c) contacting (CIV') with an activating agent and optionally a base (B1);
- (d) reacting with malonate monoester (MME) and a divalent metal;
- (e) contacting with an acid (A2); and
- (f) contacting with a base (B2) in the presence of a 1-4C alcohol, tetrahydrofuran or dimethylformamide.

R1, R2 = 1-6C alkyl, cyclohexyl, phenyl or CH<sub>2</sub>CH<sub>2</sub>Ar;

Ar = phenyl substituted by R11;

R11 = optionally protected hydroxy, optionally protected amino, H, NHCOMe or N(COMe)<sub>2</sub>.

INDEPENDENT CLAIMS are also included for the following:

- (A) preparation of (CVI) in which steps (a) - (c) are replaced by contacting (CIV), or its free acid form, with an activating agent;
- (B) (R)-3-hydroxy-3-(2-phenylethyl)hexanoic acid (CIV'a) and its salts (preferably the hydroxide, ammonia, tromethamine (THAM) 2-amino-2-hydroxymethyl-1,3-propanediol, (1R,2S)- or (1S,2R)-norephedrine, (R)- or (S)-2-amino-2-phenylethanol, or (R) or (S)-1-phenylethylamine salt);
- (C) (6R)-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one (CVIa);
- (D) (3 alpha (R), 6(R))-5,6-dihydro-4-hydroxy-3-(1-(3-nitrophenyl))-

propyl)-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one (XVII);  
 (E) (S)-methyl 3-(3-nitrophenyl)pentanoate (XIII); and  
 (F) (3 alpha (R),6(R))-5,6-dihydro-4-hydroxy-3-((Z)-1-(3-nitrophenyl)propenyl)-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one (XXV).

USE - The compounds are intermediates for (R-(R(asterisk)),R(asterisk))-N-(3-(1-(5,6-dihydro-4-hydroxy-2-oxo-(6-(2-phenylethyl)-6-propyl-2H-pyran-2-yl)propyl)phenyl)-5-trifluoromethyl-2-pyridinesulfonamide (XIX) useful as a retroviral protease inhibitor for treating human **immunodeficiency** virus (HIV) (see WO9230670 and WO9411361), human T-cell leukemia virus, and symptomatic acquired immune deficiency syndrome (AIDS).

(CVIa) is an intermediate for (XXV) which is an intermediate for (XVII) which is an intermediate for (XIX).

ADVANTAGE - The process produces (CVI) in optically pure form.

Dwg.0/0

L41 ANSWER 7 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 1995-284907 [38] WPIX

DOC. NO. NON-CPI: N1995-216913

DOC. NO. CPI: C1995-128577

TITLE: Quaternary ammonium conjugates for use in **immunoassays** - also for eliciting antibodies and determination of hapten(s) contg. a **tertiary amine**, e.g. drugs of abuse.

DERWENT CLASS: B04 B05 D16 S03

INVENTOR(S): CRAIG, A R

PATENT ASSIGNEE(S): (DADE-N) DADE CHEMISTRY SYSTEMS INC; (DUPO) DU PONT DE NEMOURS & CO E I; (DADE-N) DADE BEHRING INC

COUNTRY COUNT: 5

PATENT INFORMATION:

| PATENT NO   | KIND | DATE     | WEEK      | LA | PG |
|-------------|------|----------|-----------|----|----|
| EP 668504   | A1   | 19950823 | (199538)* | EN | 20 |
| R: DE FR IT |      |          |           |    |    |
| JP 07260784 | A    | 19951013 | (199550)  |    | 14 |
| US 5492841  | A    | 19960220 | (199613)  |    | 10 |
| JP 2731739  | B2   | 19980325 | (199817)  |    | 13 |
| EP 668504   | B1   | 20010321 | (200117)  | EN |    |
| R: DE FR IT |      |          |           |    |    |
| DE 69520383 | E    | 20010426 | (200130)  |    |    |

APPLICATION DETAILS:

| PATENT NO   | KIND | APPLICATION    | DATE     |
|-------------|------|----------------|----------|
| EP 668504   | A1   | EP 1995-101210 | 19950130 |
| JP 07260784 | A    | JP 1995-29300  | 19950217 |
| US 5492841  | A    | US 1994-199380 | 19940218 |
| JP 2731739  | B2   | JP 1995-29300  | 19950217 |
| EP 668504   | B1   | EP 1995-101210 | 19950130 |
| DE 69520383 | E    | DE 1995-620383 | 19950130 |
|             |      | EP 1995-101210 | 19950130 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|-----------|------|-----------|
|-----------|------|-----------|

JP 2731739 B2 Previous Publ. JP 07260784  
DE 69520383 E Based on EP 668504

PRIORITY APPLN. INFO: US 1994-199380 19940218

AN 1995-284907 [38] WPIX

AB EP 668504 A UPAB: 19960829

Quaternary ammonium conjugate of formula (I), are useful in **immunoassays** and/or eliciting antibodies for determining the presence and/or amt. of a hapten in a test sample. The hapten has a **tert. amine** gp. or can be derivatised to a **tert. amine** gp.. [(Q+-L-Z-)-M]B- (I). Q = a quat. ammonium gp. cyclic or acyclic, contg. a **tert. amine** gp. present in the hapten or its deriv.; L = a linker contg. 0-20C and hetero atoms arranged in a chain and/or ring structure provided that there are not more than 6 heteroatoms and that not more than 2 are linked in sequence; Z = -C=O-, -CH=, -N=N-, -NH-, -NMe-, -NH-S=C-, -SO2-, -OC=O- or -C=O-NH-NH2-; x = 1; and B = an anion. In the subsequent prepn. claim, the link to the carrier (L-Z) has 0-40C and heteroatoms. Also claimed is an antibody raised against the conjugate (I).

USE - (I) is of use in **assay** of drugs contg. a **tert. amine** gp. or those which can be derivatised to a **tert. amine** gp. This gp. can be quaternised and linked to the carrier to provide (I). The drugs include drugs of abuse, e.g. amphetamines, barbiturates, benzodiazepams, cocaine, methadone, methaqualone, opiates, phencyclidine, propoxyphene, tetrahydrocannabinol and their related structures; also other drugs, e.g. quinidine, procainamide and N-acetylprocainamide or tricyclic amine antidepressants. Detection and determ. of these is either by conjugation with an **immunogen** for an **immunoassay** or with a reporter contg. gp., e.g. fluorescent or chemiluminescent. The **immunoassays** include ELISA, sandwich, fluorescence polarisation, nephelometric or **particle based agglutination** types. (I) can also be injected into animal hosts to stimulate antibody prodn. and the latter harvested for use in binding reactions, opt. after purificn. by e.g. affinity chromatography with haptens for their detection and determination with high specificity.

ADVANTAGE - (I) are stated to offer significant advantages over known **immunogenic** conjugates and reporter reagents, without these being specified.

Dwg.0/0

ABEQ US 5492841 A UPAB: 19960329

A quaternary ammonium conjugate useful for eliciting antibodies to a non-quaternary ammonium hapten or in an **immunoassay** for determining the presence and/or amount in a test sample of a non-quaternary ammonium hapten, the quaternary ammonium conjugate comprising compounds of the formula ((Q(+)-L-Z)xM) B- wherein

Q+ is a quaternary ammonium group, cyclic or acyclic, derived by covalent attachment of a linker to a hapten selected from the group consisting of cocaine, methadone, methaqualone, propoxyphenes, phencyclidine, amphetamine, benzodiazepams, quinidine, procainamide, N-acetyl procainamide, and tricyclic amines; L is a linker comprising from 0 to 20 carbon atoms and heteroatoms arranged in a straight or branched chain and/or containing ring structures, with no more than a total of 6 heteroatoms and with no more than two heteroatoms linked in sequence; Q+ is linked to L at the **tertiary amine** group of the hapten; -Z- is a residue group selected from the group consisting of -C=O,

-CH=, -N=N-, -NH-, -NCH<sub>3</sub>, -NH-S=C, -SO<sub>2</sub>-, -O-C=O, and -C=O-NH-NH<sub>2</sub>-; x is greater than or equal to 1; M is a carrier selected from the group consisting of poly(amino)acids, carbohydrates, yeasts, polysaccharides and solid phase particles; B- is an anion; and (Q(+)-L-Z)x- is covalently bound to M.

Dwg.0/0

L41 ANSWER 8 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 1986-260397 [40] WPIX

DOC. NO. NON-CPI: N1986-194558

DOC. NO. CPI: C1986-112598

TITLE: Prepn. of carriers for enzyme **immunoassay** - by treating polyacrylamide holding antigen or antibody with carbo di imide and guanidine salt or urea.

DERWENT CLASS: A96 B04 D16 S03

PATENT ASSIGNEE(S): (IGAK-N) IGAKU SEIBUTUGAKU K

COUNTRY COUNT: 1

PATENT INFORMATION:

| PATENT NO   | KIND | DATE     | WEEK      | LA | PG |
|-------------|------|----------|-----------|----|----|
| JP 61186857 | A    | 19860820 | (198640)* |    | 5  |
| JP 05064739 | B    | 19930916 | (199341)  |    | 5  |

APPLICATION DETAILS:

| PATENT NO   | KIND | APPLICATION   | DATE     |
|-------------|------|---------------|----------|
| JP 61186857 | A    | JP 1985-28546 | 19850214 |
| JP 05064739 | B    | JP 1985-28546 | 19850214 |

FILING DETAILS:

| PATENT NO   | KIND       | PATENT NO   |
|-------------|------------|-------------|
| JP 05064739 | B Based on | JP 61186857 |

PRIORITY APPLN. INFO: JP 1985-28546 19850214

AN 1986-260397 [40] WPIX

AB JP 61186857 A UPAB: 19930922

The process comprises treating carrier of polyacrylamide holding an antigen or antibody with one or two of the cpds. of formula R<sub>1</sub>-N=C=N-R<sub>2</sub>R<sub>3</sub> (I), and then treating the carrier with a guanidine salt or urea (where R<sub>1</sub> is a monovalent hydrocarbon gp.; R<sub>2</sub> is a divalent hydrocarbon gp.; R<sub>3</sub> binding to R<sub>2</sub> represents amino forming a **tert-amine**).

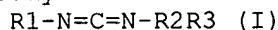
Enzyme **immunoassay** comprises binding an antibody or antigen to be **assayed** to the first antigen or antibody held on the carrier, then binding a prefixed amt. of enzyme-labelled 2nd antigen or antibody to the antibody or antigen bound to the carrier, and measuring the activity of the 2nd antigen or antibody bound or not bound to the carrier.

Polyacrylamide as carrier may be used in a large-surface form, e.g. granules, pieces, fibre, partic. gelled polyacrylamide used in gel column chromatography. Use of **carbodiimides** (I) is effective in fixing an antigen or antibody on the carrier. The antigen or antibody-fixed carrier is further treated with guanidine hydrochloride or urea for further stabilisation.

ADVANTAGE - Any antigen or antibody can be fixed stably on the carriers. Stable and qualified carriers used in enzyme **immunoassay** can be prepd. on a large scale. By using the carriers, enzyme **immunoassay** (EIA) can be made accurately with reduced error.  
0/0

ABEQ JP 93064739 B UPAB: 19931130

Process comprises treating carrier of polyacrylamide holding an antigen or antibody with one or two of the cpds. of formula



and then treating the carrier with a guanidine salt or urea. In (I), R1 is a monovalent hydrocarbon gp.; R2 is a divalent hydrocarbon gp.; R3 binding to R2 represents amino forming a **tert.-amine**.

Enzyme **immunoassay** comprises binding an antibody or antigen to be **assayed** to the first antigen or antibody held on the carrier, then binding a prefixed amt. of enzyme-labelled 2nd antigen or antibody to the antibody or antigen bound to the carrier, and measuring the activity of the 2nd antigen or antibody bound or not bound to the carrier.

Polyacrylamide as carrier may be used in a large-surface form, e.g., granules, pieces, fibre, partic. gelled polyacrylamide used in gel column chromatography. Use of **carbodiimides** (I) is effective in fixing an antigen or antibody on the carrier. The antigen or antibody-fixed carrier is further treated with guanidine hydrochloride or urea for further stabilisation.

ADVANTAGE - Any antigen or antibody can be fixed stably on the carriers. Stable and qualified carriers used in enzyme **immunoassay** can be prepd. on a large scale. By using the carriers, enzyme **immunoassay** (EIA) can be made accurately with reduced error.  
(J61186857-A)

L41 ANSWER 9 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 1986-172184 [27] WPIX

CROSS REFERENCE: 1995-390286 [50]

DOC. NO. NON-CPI: N1986-128520

DOC. NO. CPI: C1986-073971

TITLE: Immune body-adsorbent prepn. - by reducing sulphur-sulphur bond in antibody then crosslinking with binding gp of carrier.

DERWENT CLASS: A96 B04 D16 S03

PATENT ASSIGNEE(S): (ORIY) ORIENTAL YEAST CO LTD

COUNTRY COUNT: 1

PATENT INFORMATION:

| PATENT NO   | KIND | DATE     | WEEK      | LA | PG |
|-------------|------|----------|-----------|----|----|
| JP 61103838 | A    | 19860522 | (198627)* |    | 8  |
| JP 07053759 | B2   | 19950607 | (199527)  |    | 4  |

APPLICATION DETAILS:

| PATENT NO   | KIND | APPLICATION    | DATE     |
|-------------|------|----------------|----------|
| JP 61103838 | A    | JP 1984-225938 | 19841029 |
| JP 07053759 | B2   | JP 1984-225938 | 19841029 |

FILING DETAILS:



| PATENT NO   | KIND        | PATENT NO   |
|-------------|-------------|-------------|
| JP 07053759 | B2 Based on | JP 61103838 |

PRIORITY APPLN. INFO: JP 1984-225938 19841029

AN 1986-172184 [27] WPIX

CR 1995-390286 [50]

AB JP 61103838 A UPAB: 19951221

S-S bond in the hinge part of an antibody is reduced, and the SH gp. in the resulting SH-contg. antibody is crosslinked with a binding gp. of a carrier to obtain an immune body-adsorbent.

The SH-contg. antibody is crosslinked with the SH gp. in the SH-contg. carrier in the presence of a cpd. having two or more maleimido gps. in one molecule. Alternatively SH-contg. antibody is crosslinked with the binding gp. in a carrier contg. one or more binding gps. of amino., imino, hydrazino, and prim. to **tert. amine** in the presence of a cpd. having both maleimido group and succinimido -ester gp. in one molecule.

Carriers are polysaccharides (agarose, sepharose, dextran, cellulose), synthetic resins (polystyrene, polyacrylamide, biogel, polyvinyl), glass or silica, kaolin, carbon, bentonite, yarn, wood, microorganisms, red blood cells of animals.

USE/ADVANTAGE - The antigen-bindability is high. Used as a carrier in **immunoaffinity** chromatography, a solid phase in enzyme-immunoassay, immuno-sensor, a **latex** in latex-agglutination reaction, etc.

0/0

Dwg. 0/0